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ORIGINAL RESEARCH

Association of the High-Sensitivity C-Reactive Protein-to-Albumin Ratio with Carotid Atherosclerotic Plaque: A Community-Based Cohort Study

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Background: The inflammatory response is a pivotal factor in accelerating the progression of atherosclerosis. The high-sensitivity C-reactive protein-to-albumin ratio (CAR) has emerged as a novel marker of systemic inflammation. However, few studies have shown the CAR to be a promising prognostic marker for carotid atherosclerotic disease. This study aimed to analyse the predictive role of the CAR in carotid atherosclerotic disease.

Methods: This community-based cohort study recruited 2003 participants from the Rose asymptomatic IntraCranial Artery Stenosis (RICAS) study who were free of stroke or transient ischemic attack. Carotid atherosclerotic plaques and their stability were identified via carotid ultrasound. Logistic regression models were utilized to investigate the association between CAR and the presence of carotid atherosclerotic plaques.

Results: The prevalence of carotid atherosclerotic plaques was 38.79% in this study. After adjusting for clinical risk factors, including sex, age, dyslipidemia, hypertension, diabetes mellitus (DM), and smoking and drinking habits, a high CAR-level was independently associated with carotid plaque (odds ratio [OR] of upper: 1.46, 95% confidence interval [CI]: 1.13–1.90, $P = 0.004$; P for trend = 0.011). The highest CAR tertile was still significantly associated with carotid plaques among middle-aged (40–64 years) or female participants. Notably, an elevated CAR may be an independent risk factor for vulnerable carotid plaques (OR of upper: 2.06, 95% CI: 1.42–2.98, $P < 0.001$; P for trend <0.001).

Conclusion: A high CAR may be correlated with a high risk of carotid plaques, particularly among mildly aged adults (40–64 years) or females. Importantly, the CAR may be associated with vulnerable carotid plaques, suggesting that the CAR may be a new indicator for stroke prevention.

Keywords: C-reactive protein, albumin, plaque, atherosclerotic, cohort study

Introduction

Stroke is the second-leading cause of both disability and death worldwide[1] and contributes to 42.2% of neurological disability-adjusted life-years (DALYs),[2] additionally, stroke poses a substantial burden at the individual and societal levels, especially in middle- and lower-income countries.[1] It has been well established that carotid atherosclerosis is a principal contributor to

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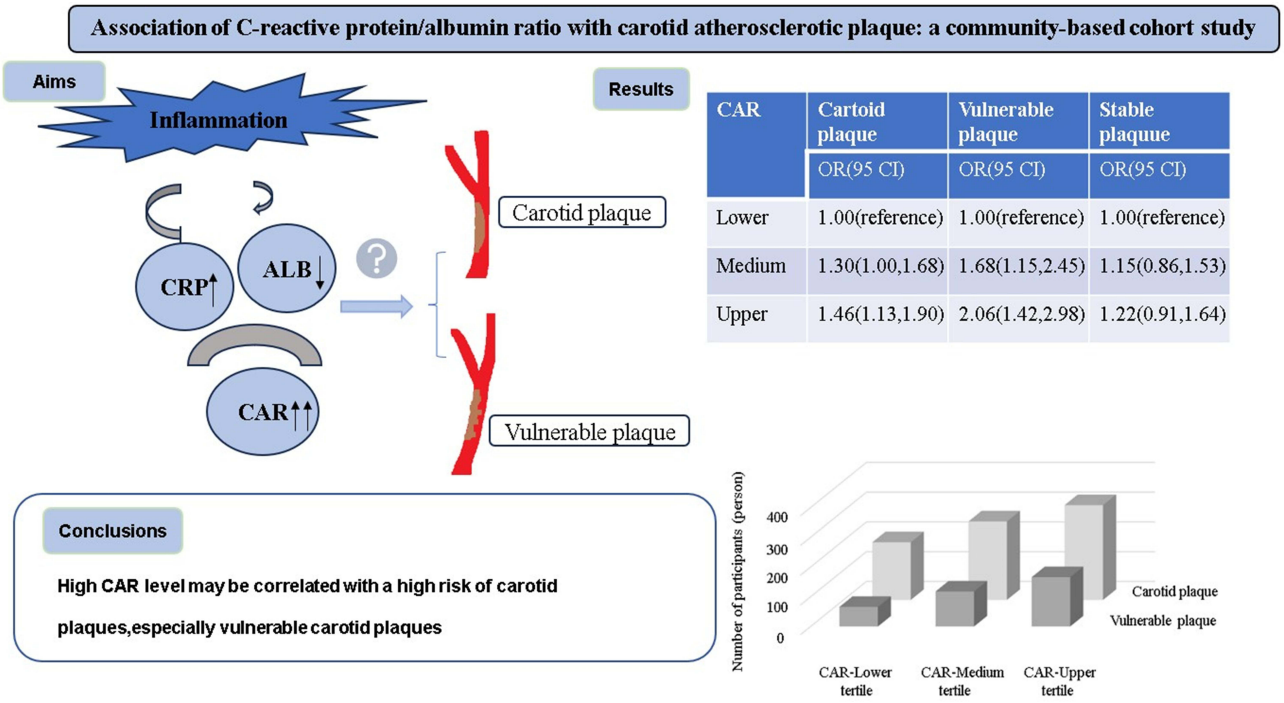
Graphical Abstract



ischemic stroke and is the most prevalent form of large vessel atherosclerotic disease.[3] Thus, identifying clinically manageable and preventive risk factors for carotid atherosclerosis is paramount in future stroke incidence.

Previous studies have highlighted the correlation between systemic inflammatory markers and carotid atherosclerosis[4] and underscored the involvement of high-sensitivity C-reactive protein (hs-CRP) and albumin (ALB) in atherosclerotic disease,[5,6] which are both synthesized by liver cells. It was generally considered that there may be a positive correlation between hs-CRP and cardiovascular disease.[7] Hs-CRP, as the most representative inflammatory marker, is integral to the inflammatory response to the process of atherosclerosis and increases during the acute phase response,[8] which may induce atherogenesis by activating the inflammatory cascade and interacting with endothelial and smooth muscle cells, leading to foam cell formation, endothelial dysfunction, and plaque destabilization.[7] Conversely, the serum ALB concentration, characterized as a negative acute-phase protein, exhibited an inverse correlation with inflammatory severity. Previous study had also revealed that low serum ALB was associated with cardiovascular disease, which exits antioxidant capacity and anticoagulant and antiplatelet activity.[9]

Furthermore, the CAR reflects the balance between hs-CRP and ALB levels, both of which facilitate atherosclerosis progression by affecting the inflammatory reaction in atherosclerosis, increasing the toxic effects of oxidized LDL.[10,11] Therefore, CAR has attracted increased interest from researchers. Emerging evidence posits CAR as a novel prognostic biomarker for mortality in critically ill patients afflicted with conditions such as coronary artery disease, cancer, endocrine disease, or young stroke.[12–15] Previous study indicated that increased serum CAR is independently correlated with the severity of carotid artery stenosis in patients who underwent carotid angiography for suspected carotid artery diseases.[16] However, as a new indicator of systemic inflammation, the association between CAR and carotid atherosclerotic plaques in rural communities without cerebrovascular symptoms remains unclear.

Therefore, in this study, we aimed to investigate whether the CAR was associated with the incidence of carotid atherosclerotic plaques and vulnerable carotid plaques among rural residents in China.

Methods

Study Design and Participants

The study participants were from the Rose asymptomatic IntraCranial Artery Stenosis (RICAS) study, which was designed as a rural community-based cohort living in Kongcun Town, Pingyin County, China. Participants focused on registered residents aged ≥40 years who were free from a history of stroke and transient ischemic attack (TIA). The RICAS study design has been described previously.[17]

In brief, in October–November 2017, 2474 rural residents completed face-to-face questionnaires and carotid ultrasound examinations at baseline. In the first stage of screening, participants were excluded if they were unable to complete baseline interview data (n=163) or clinical data (n=284). Consequently, 2027 participants completed all the required components, with subsequent exclusion of participants lacking available ultrasound data (n=24), ultimately, these requisites left 2003 participants eligible for the final analysis. Figure 1 shows the flow chart of the study population.

Covariate Collection and Assessments

Between October 2017 and October 2018, participants undertook face-to-face interviews to collect data on demographic information, socioeconomic factors, personal and family medical history, and lifestyle factors. Hypertension was defined as a systolic and/or diastolic blood pressure ≥140/90 mmHg, antihypertensive medication usage, or a self-reported history of the condition. Diabetes mellitus (DM) was characterized by a fasting blood glucose level ≥7.0 mmol/L, a self-reported history of diabetes, or the use of hypoglycemic medication. The definitions of smoking and alcohol drinking habits have been described in previous studies.[18] Other cardiovascular risk factor (CRF) analyses were also conducted at the certified clinical laboratory of Shandong Provincial Hospital, the risk factors included high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglyceride, hs-CRP, and ALB levels, which have also been carefully described in previous studies.[17]

Assessments and Definition of CAR

The CAR (mg/g) was calculated by dividing the hs-CRP (mg/L) value by the albumin level.[14] In the absence of an established clinical definition for abnormal CAR values, the CAR was subsequently classified as a categorical variable based on tertiles.

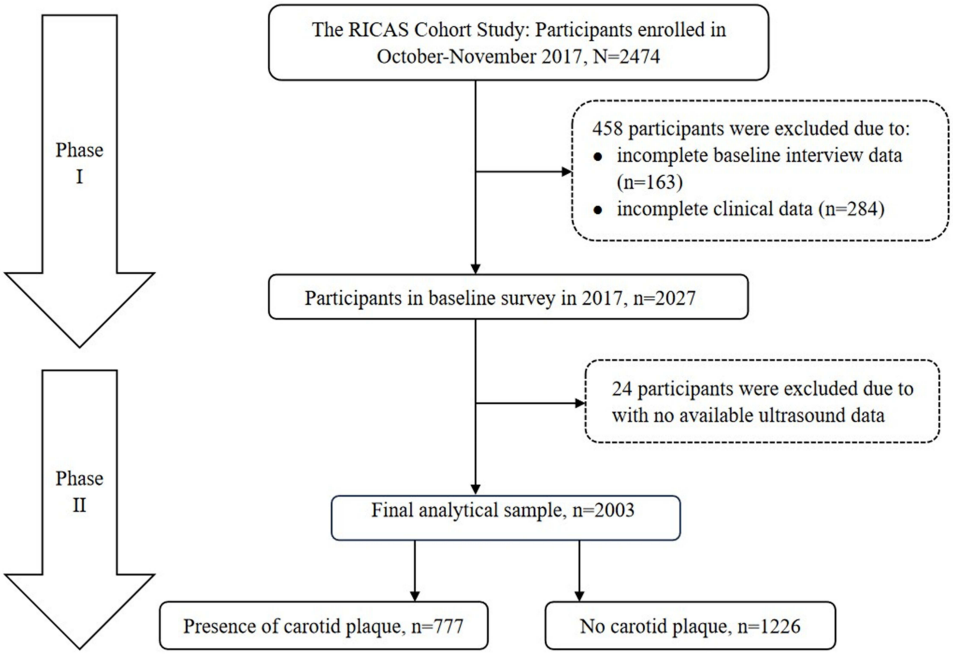


Figure 1 Flow chart of the study participants.
Abbreviations: MRI, magnetic resonance imaging; TCD, transcranial Doppler.

Detection of Carotid Atherosclerotic Plaques and Vulnerable Carotid Plaques

Carotid ultrasound examinations were conducted with participants in a head straight, flat supine position by two experienced physicians using a 7-MHz linear transducer (Siemens ACUSON P500). The specific operating methods used were described in a previous study.[19] Carotid atherosclerotic plaques were defined as those with a carotid intima-media thickness (cIMT) ≥1.5 mm in any segment of the carotid arteries.[20] Carotid atherosclerotic plaques can be categorized into hypoechoic, isoechoic, hyperechoic, and inhomogeneous-echoic plaques, with varying echoes and stabilities due to differing tissue component contents within the plaques. Hyperechoic plaques containing calcification and isoechoic plaques containing fibres tended to be stable. Vulnerable carotid plaques were defined according to the presence of hypoechoic and inhomogeneous echoic plaques containing necrotic tissue, hemorrhage, and other components in the plaques, as indicated by ultrasound.[21] Moreover, irregularly surfaced plaques were also defined as the vulnerable plaques that tend to form unstable thrombi on plaque surfaces due to either stagnant flow or exposure of the central necrotic core.[22]

Statistical Analysis

Participants were divided into two groups based on the presence or absence of plaques. Continuous variables, presented as medians and interquartile ranges (IQRs), were compared using the Kruskal–Wallis test, as all continuous variables in this study were nonnormally distributed. Categorical variables are expressed as counts and percentages (%) and were compared using chi-square tests. Logistic regression was used to evaluate the association between CAR levels and carotid atherosclerotic plaque incidence by calculating crude odds ratios (ORs) and adjusted ORs with 95% confidence intervals (CIs). The results were derived from two models: Model 1, adjusted for sex and age, and Model 2, which additionally accounted for dyslipidemia, hypertension, DM, smoking, and drinking habits. Moreover, sex and age were evaluated to assess whether there was any significant difference between CAR and carotid plaque incidence. The association between the CAR and vulnerable carotid plaques was further investigated using multiple logistic regression. All the statistical tests were 2-sided, and the significance level was set at $P < 0.05$. All the statistical analyses were performed using IBM SPSS Statistics V.26.0 for Windows.

Results

Baseline Characteristics

The study enrolled 2003 participants (mean age, 57.66 years; SD = 10.35; 48.03% men), 777 (38.79%) of whom had carotid plaque. The demographic data and clinical characteristics of all participants are detailed in Table 1. Participants with carotid plaques were older ($P < 0.001$) and had a higher BMI ($P = 0.002$). The prevalence of hypertension, diabetes, and the use of antihypertensive or glucose-lowering medications was greater among individuals with carotid plaques than among those without carotid plaques ($P < 0.001$). Compared with participants without carotid plaque, those with carotid plaque had higher levels of CRP and CAR ($P < 0.001$).

Association Between CAR and Carotid Plaques

Higher CAR was independently associated with the presence of carotid plaque, adjusted for Model 1 or Model 2 (P for trend <0.05) (Table 2). Moreover, a histogram was generated to display the distributions of carotid plaques and vulnerable plaques among the participants with different CAR counts (Figure 2).

Subsequent analyses stratified by common risk factors, including age and sex, were performed to investigate the association between baseline CAR and carotid plaque incidence (Table 2). Within age-stratified analyses, baseline CAR levels were significantly associated with the prevalence of carotid plaque among the middle-aged adults group (multivariate-adjusted, OR of upper: 1.44, 95% CI: 1.05–1.99, $P = 0.024$; P for trend = 0.061); however, this correlation was absent in the older aged adults group (OR of upper: 1.35, 95% CI: 0.84–2.19, $P = 0.216$; P for trend = 0.128), which suggests that elevated baseline CAR levels were significantly associated with the high risk of carotid plaque exclusively in middle-aged adults, not in older individuals. According to the sex-stratified analyses, higher baseline CAR levels were significantly correlated with an increased risk of carotid plaque only among females (OR of upper: 1.46, 95% CI: 1.13–1.90, $P = 0.004$; P for trend = 0.011) but not males (OR of upper: 1.26, 95% CI: 0.86–1.85, $P = 0.230$; P for trend = 0.255).

Table 1 Baseline Characteristics of Study Participants

Characteristics	Total Sample (n=2003)	Carotid Plaque		
		No (n=1226)	Yes (n=777)	*p*-value
Age (years)	56(49–65)	52(47–60)	63(55–71)	<0.001
Male, n (%)	962(48.03)	566(46.17)	396(50.97)	0.036
BMI (kg/m^2)	25.00(22.77–27.27)	25.08(23.00–27.44)	24.77(22.38–26.89)	0.002
Smoking, n (%)	453(22.62)	248(20.23)	205(26.38)	0.001
Alcohol drinking, n (%)	657(32.80)	400(32.63)	257(33.08)	0.845
Dyslipidemia, n (%)	800(39.94)	434(35.40)	366(47.10)	<0.001
Hypertension, n (%)	1153(57.56)	592(48.29)	561(72.20)	<0.001
Diabetes mellitus, n (%)	305(15.23)	137(11.17)	168(21.62)	<0.001
Use of antihypertensive medication, n (%)	326(16.28)	128(10.44)	198(25.48)	<0.001
Use of glucose-lowering medications, n (%)	137(6.84)	56(4.57)	81(10.42)	<0.001
hs-CRP (mg/L)	0.66(0.26–1.57)	0.51(0.21–1.35)	0.86(0.37–2.04)	<0.001
ALB (g/L)	45.20(43.20–47.00)	45.30(43.30–47.10)	45.00(43.10–46.80)	0.059
CAR (mg/g)	0.01(0.01–0.03)	0.01(0.00–0.03)	0.02(0.01–0.05)	<0.001

Notes: Data was shown as numbers (%) and median (25–75 percentiles). Comparison according to carotid plaque using Mann–Whitney *U*-test and χ^2 test appropriately.

Abbreviations: BMI, body mass index; hs-CRP, high-sensitivity C-reactive protein; ALB, albumin.; CAR, high-sensitivity C-reactive protein to albumin ratio.

Table 2 Association of CAR with Carotid Plaque

CAR (mg/g)	n/N	Model 1		Model 2	
		OR (95% CI)	*P* value	OR (95% CI)	*P* value
Total sample (n=2003)					
Tertiles					
Lower	194/668	1.00(reference)		1.00(reference)	
Medium	264/668	1.45(1.13,1.87)	0.004	1.30(1.00,1.68)	0.050
Upper	319/667	1.68(1.31,2.17)	<0.001	1.46(1.13,1.90)	0.004
P for trend			<0.001		0.011
Age <65 years (n=1458)					
Tertiles					
Lower	115/541	1.00(reference)		1.00(reference)	
Medium	149/489	1.55(1.15,2.09)	0.004	1.37(1.01,1.86)	0.044
Upper	150/428	1.72(1.27,2.35)	0.001	1.44(1.05,1.99)	0.024
P for trend			0.003		0.061
Age ≥65 years (n=545)					
Tertiles					
Lower	79/127	1.00(reference)		1.00(reference)	
Medium	115/179	1.13(0.70,1.84)	0.610	1.00(0.61,1.64)	0.991
Upper	169/239	1.43(0.90,2.27)	0.132	1.35(0.84,2.19)	0.216
P for trend			0.116		0.128
Male (n=962)					
Tertiles					
Lower	114/374	1.00(reference)		1.00(reference)	
Medium	135/314	1.31(0.92,1.86)	0.136	1.13(0.79,1.63)	0.504
Upper	147/274	1.49(1.03,2.16)	0.035	1.26(0.86,1.85)	0.230
P for trend			0.053		0.255

(*Continued*)

Table 2 (Continued).

CAR (mg/g)	n/N	Model 1		Model 2	
		OR (95% CI)	*P* value	OR (95% CI)	*P* value
Female (n=1041)					
Tertiles					
Lower	80/294	1.00(reference)		1.00(reference)	
Medium	129/354	1.61(1.11,2.33)	0.012	1.30(1.00,1.68)	0.050
Upper	172/393	1.86(1.30,2.66)	0.001	1.46(1.13,1.90)	0.004
P for trend			0.004		0.011

Notes: OR and 95% CIs were calculated by logistic regression. Model 1 was adjusted for age, sex; Model 2 was additionally adjusted for dyslipidemia, smoking, drinking, hypertension, and diabetes mellitus. n/N indicates number of carotid plaque/number of participants.
Abbreviations: OR, odds ratio; CI, confidence interval.

Association Between CAR Levels and Vulnerable Carotid Plaques

The association between CAR and vulnerable carotid plaques is shown in Table 3. Increased CAR levels were identified as an independent risk factor for vulnerable carotid plaques (odds ratio (OR) of upper: 2.06, 95% CI: 1.42–2.98, $P < 0.001$; P for trend <0.001). Notably, that association was not observed in participants with stable carotid plaques.

Discussion

In this rural community-based study, it was found that high CAR level might be independently associated with an increased incidence of carotid plaque, even after adjusting for several clinical risk factors. Moreover, a high CAR level might be significantly associated with carotid plaque in mildly aged or female participants but not in older or male participants. More importantly, CAR may be an independent risk factor for vulnerable carotid plaque. Based on the findings of the present study, the CAR might serve as a clinical screening target to identify individuals at higher risk for carotid plaque, particularly those with vulnerable carotid plaque. To our knowledge, this is the first study to investigate the association between CAR and carotid atherosclerotic plaques in a rural community population.

Hs-CRP is a protein that increases during the acute phase response and the serum ALB is a negative acute-phase protein. Therefore, CAR, as a novel serum inflammatory marker with good biological stability, may be superior to CRP or ALB alone. CAR is inexpensive, quickly calculated, and routinely available.[23] Recent studies in literature focused on the association between CAR and the effective indicator for evaluating the prognosis of various diseases, for example, hepatitis[24] and COVID-19 disease.[23] The relationship between CAR and cardiovascular disease has been investigated in some studies, which include left ventricular thrombus formation in patients with acute anterior myocardial infarction[25]

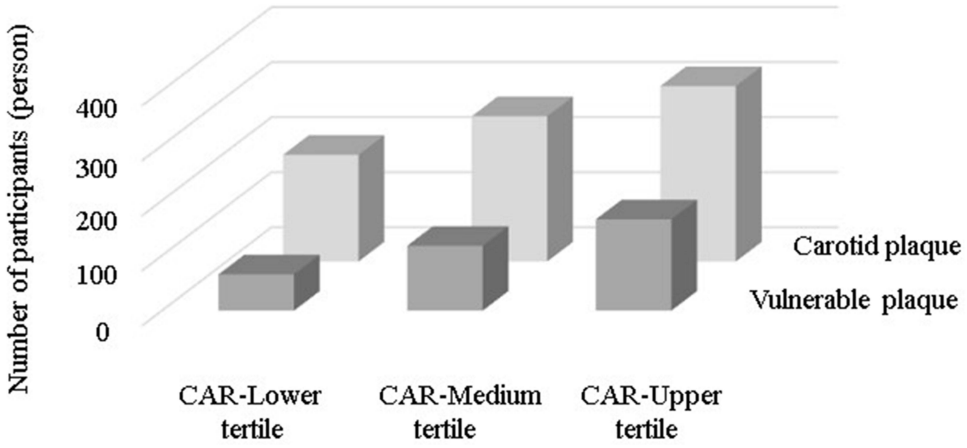


Figure 2 The participants distribution of carotid plaque and vulnerable plaque in different CAR levels.

Table 3 Association of CAR with Stable and Vulnerable Plaque

CAR (mg/g), Tertiles	Carotid Plaque					
	Vulnerable			Stable		
	n	OR (95% CI)	*P* value	n	OR (95% CI)	*P* value
Lower	66	1.00(reference)		128	1.00(reference)	
Medium	118	1.68(1.15,2.45)	0.007	146	1.15(0.86,1.53)	0.342
Upper	166	2.06(1.42,2.98)	<0.001	153	1.22(0.91,1.64)	0.188
P for trend			<0.001			0.235

Note: OR and 95% CI were estimated from the multivariable logistic regression models that were adjusted for sex, age, dyslipidemia, smoking, drinking, hypertension, and diabetes mellitus.
Abbreviations: OR, odds ratio; CI, confidence interval.

and coronary artery disease severity in patients with acute coronary syndrome.[7] Previous study also revealed that there may be a partial relationship between CAR and cIMT in psoriasis.[26] Another study revealed that a significantly increased CAR was independently associated with an increased risk of adverse outcomes in young patients with stroke,[14] which suggested that there may be some potential mechanisms linking CAR and carotid atherosclerosis. However, studies on the use of CAR for assessing cerebrovascular diseases, particularly the association between CAR and carotid atherosclerosis plaques, have rarely involved rural participants.

Inflammation has an important role to play in all stages of atherosclerosis.[4] The association between hs-CRP and carotid atherosclerosis was discovered in a retrospective cohort study.[5] Hs-CRP, produced in hepatocytes and a marker of an intense inflammatory response, may accelerate the atherosclerotic process by directly fostering endothelial cell activation, adhesion molecule expression, and resultant dysfunction.[7,26] It might also promote the uptake of oxidized LDL into endothelial cells, inducing endothelial dysfunction through the ligand-binding domain of hs-CRP binding to the LDL-C scavenger receptor.[11,27] Similarly, ALB, which is synthesized by hepatocytes and influenced by inflammatory and nutritional levels[28] and is expressed as a negative acute-phase protein that is negatively correlated with the severity of inflammation, has been associated with atherosclerosis due to its ability to maintain osmotic pressure, resist blood stagnation and thrombosis, and provide antioxidant effects as the primary antioxidant in the human body.[28,29] CAR, reflecting combined hs-CRP and ALB levels, may contribute to the development of atherosclerosis through these mechanisms, potentially through intrinsic inflammatory processes within atherosclerotic plaques. In this community-based cohort study, there was a positive relationship between CAR and carotid atherosclerotic plaques, which suggests that in addition to paying attention to the hs-CRP, we also need to consider the nutritional status, especially among rural residents.

In addition, we detected the relationship between CAR and age on carotid plaques. A positive association between CAR and carotid atherosclerotic plaques may exist in middle-aged adults. Our study was consistent with a previous study that identified trends toward increasing stroke incidence at younger ages, particularly in developing countries.[30,31] This association may be due to several factors. Firstly, the middle-aged adults have a high proportion of modifiable lifestyle risk factors, such as decreased physical activity or polysubstance abuse. Additionally, middle-aged adults are more likely to have less common stroke etiologies, including arterial dissection, inflammatory and non-inflammatory arteriopathies, hypercoagulable states, high-risk patent foramen ovale, and genetic factors. More importantly, middle-aged adults are more likely to exhibit an unusual stroke of infectious vasculitis, which includes infectious vasculitis associated with human immunodeficiency virus (HIV), varicella zoster virus (VZV), syphilis, and inflammatory vasculopathy such as Cogan syndrome and Susac syndrome.[32] Furthermore, our study revealed a significant correlation between CAR and carotid atherosclerotic plaques in females. A previous study indicated a higher incidence of stroke among older female participants.[33] Estrogens and progestins can suppress the release of inflammatory mediators in microglia and reduce neuronal cell death. This suggests that anti-inflammatory phenotype in females may be driven by female sex hormones.[34] Most females in the present study tended to be postmenopausal due to demographic characteristics. Therefore, they lose the protection of estrogen while estrogen slows the atherosclerosis process by affecting the synthesis of collagen and the

degradation of elastin.[35] Meanwhile, loss of estrogen in middle-aged females is believed to drive this increase in abdominal adiposity, adipose inflammation, and insulin resistance. This may predispose females to a higher risk of developing atherosclerosis.[36]

A previous study established that vulnerable carotid plaques contribute to 15–20% of ischemic strokes.[37] The pathogenic mechanism of carotid atherosclerotic plaque appears to involve both chronic hypoperfusion and microembolic events. Vulnerable plaques, characterized by high lipid content, thin fibrous caps, and neovascularization,[38] are more prone to rupture, leading to microembolic events. A recent single-center, hospital-based, cross-sectional study demonstrated a link between elevated CAR level and increased risk of adverse outcomes in patients with stroke,[14] suggesting a potential association with vulnerable carotid plaques. This study first analysed how a high CAR-level was independently associated with a high incidence of carotid vulnerable plaque. The potential mechanism underlying the association between high CAR and vulnerable carotid plaques can be explained by affecting the inflammatory reaction in atherosclerosis, increasing the toxic effects of oxidized LDL and accelerating the atherogenic process.

This is the first study to investigate the association between CAR and carotid atherosclerotic plaques. Moreover, the correlation between the CAR and carotid atherosclerotic plaque was detected via carotid ultrasound, which can be used to measure carotid plaque in a simple, non-invasive, and reproducible manner. Furthermore, this was a large-sample cross-sectional study based on a natural population.

Nonetheless, the present study has several limitations. First, as a single-center study, its findings may not be widely generalizable. Second, this study did not perform pathology or high-resolution magnetic resonance imaging (HR-MRI) to assess carotid atherosclerotic plaque size, irregular shape, or area or the composition of the carotid plaque, these factors should also be taken into consideration. Furthermore, multicenter and prospective studies are necessary to further investigate the underlying mechanisms of CAR in the identification of carotid atherosclerotic plaques. Meanwhile, more research is needed to determine which inflammatory markers play a more important role in the progression of atherosclerosis.

Conclusion

This community-based cohort study revealed that a high CAR might be significantly associated with carotid plaque in mildly aged adults and female participants. More importantly, an increased CAR might be associated with vulnerable carotid plaques, suggesting that this parameter is a novel indicator for stroke prevention. These findings showed the necessity for further exploration in prospective studies in the Chinese population.

Abbreviations

CAR, High-sensitivity C-reactive protein/albumin ratio; Hs-CRP, High-sensitivity C-reactive protein; LDL, Low-density lipoprotein cholesterol; IQR, Interquartile range; OR, odds ratio.

Data Sharing Statement

The raw data supporting the conclusions of this article will be made available by the corresponding author.

Ethics Statement

The RICAS study was approved by the Ethical Standards Committees of Human Experimentation in Shandong Provincial Hospital, Shandong University. The medical research principles of the Helsinki Declaration include a code of conduct, and an informed consent form was signed by each participant after being informed of the purpose of this study.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no competing interests in this work.

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